NMR SPECTROSCOPIC INVESTIGATION OF *p*-SUBSTITUTED 2,4,4,6-TETRAPHENYL-1,4-DIHYDROPYRIDINES AND THEIR OXA AND THIA ANALOGUES

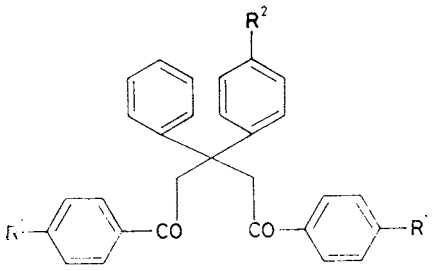
Marián SCHWARZ, Petr TRŠKA and Josef KUTHAN

Department of Organic Chemistry,
Prague Institute of Technology, 166 28 Prague 6

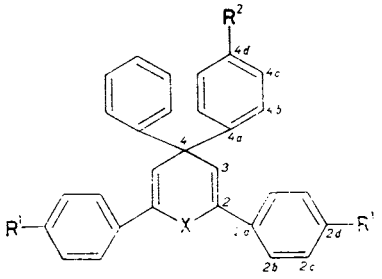
Received July 29, 1988
Accepted October 10, 1988

The ^1H, ^{13}C and ^{19}F NMR spectra of photochromic *p*-substituted 2,4,4,6-tetraphenyl-1,4-dihydropyridines *IIa—IIg*, 1-methyl-2,4,4,6-tetraphenyl-1,4-dihydropyridines *IIIa—IIIg*, 2,4,4,6-tetraphenyl-4*H*-pyrans *IVa—IVh*, and 2,4,4,6-tetraphenyl-4*H*-thiopyran *V* were inspected; it was found that compounds *IIa—IIg* occur in a dynamic equilibrium with their dihydro tautomer-*VIa—VIg*. Also deuteriodeprotonation of *IIa* and *IIa* and their reaction with trifluoroacetic acid were investigated by NMR spectroscopy.

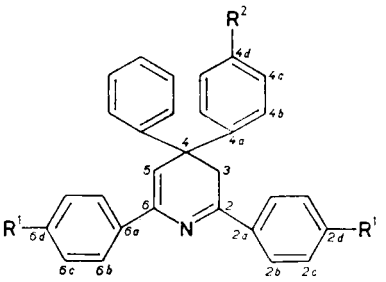
In continuation of our programme on heterocycles of types *II—V*, which were prepared from the corresponding synthons[1] related to pentanedione of type *I*, we were interested in the structure of their forms in solution. Although NMR spectroscopy has successfully been employed in structural studies of dihydropyridines[2,3] and 4*H*-pyrans[4], still no attention has been paid to detailed assignment of all signals, especially in the aromatic region of the above-mentioned tetraphenyl-substituted heterocycles. This paper concerns, therefore, mainly the interpretation of NMR spectra of compounds under study.



Ia - Ih

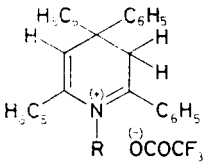


IIa - IIg, X = NH
IIIa - IIIg, X = NCH_3
IVa - IVh, X = O
V, X = S; $R^1 = R^2 = H$

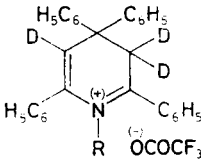


VIa–VIg

In formulae *I–IV* and *VI*: *a*, $R^1 = R^2 = H$ *b*, $R^1 = H$; $R^2 = CH_3$ *c*, $R^1 = H$; $R^2 = Cl$ *d*, $R^1 = H$; $R^2 = Br$ *e*, $R^1 = CH_3$; $R^2 = H$ *f*, $R^1 = Br$; $R^2 = H$ *g*, $R^1 = F$; $R^2 = H$ *h*, $R^1 = CH_3O$; $R^2 = H$



VII a, R = H
VII b, R = CH_3



X a, R = D
X b, R = CH_3

EXPERIMENTAL

Melting points were measured on a Boëtius micro hot-stage, the IR spectra of chloroform solutions were taken with a Perkin–Elmer, model 325 spectrophotometer, the NMR spectra of $CDCl_3$ (compounds *IIa–IIg* in $C_6D_5CD_3$, *IIa*, *IIIa*, *Va* also in $(CD_3)_2SO$) solutions were recorded with a Bruker AM-400 spectrometer. Internal references: tetramethylsilane for ^1H and ^{13}C spectra and trifluorchloromethane for ^{19}F NMR spectra; experimental parameters: 400·134 MHz, digital resolution 0·184 Hz per point, pulse length 4 μs (45°), temperature 297 K (for *IIa–IIg* 297, 320, 344, and 373 K) for ^1H NMR; 100·61 MHz, digital resolution 0·9 Hz per point, temperature 297 K, APT technique, for ^{13}C NMR, and 376·477 MHz, digital resolution 0·95 Hz per point, temperature 297 K for ^{19}F NMR.

Compounds *I–V* were synthesized by application of the process[4] as follows: 1,5-pentanediones *Ia–Ih* from the substituted acetophenone with the substituted benzophenone via ketolization, using sodium amide (procedure *C*), dihydropyridines *IIa–IIg* and *IIIa–IIIg* from the corresponding 1,5-pentanediones and ammonium acetate or methylammonium acetate in acetic acid (procedure *C*) and 4*H*-pyrans *IVa–IVh* from the respective 1,5-pentanediones by dehydratation with *p*-toluenesulfonic acid as catalyst in toluene (procedure *D*). The 4*H*-thiopyran *V* was obtained by reacting pentanedione *Ia* with phosphorus pentasulfide in xylene (analogy of procedure *A*). The physicochemical characteristics and IR spectral data of *IIb–IIg*, *IIIb–IIId*, *IIIg*, *IVb–IVd*, *IVg*, and compound *V* (the latter being already described[5,6]) are listed in Table I.

TABLE I

Characteristic data of compounds *IIb*—*IIg*, *IIIb*—*IIId*, *IIIg*, *IVb*—*IVd*, *IVg*, and *V*

Compound R^1, R^2	M.p., °C Yield, %	Formula (M.w.)	Calculated/Found % C	% H	% N	% X[a]	IR, $\tilde{\nu}$, cm^{-1} Skelet	N–H (C–O)
IIb	160—164	$C_{30}H_{25}N$	90·19	6·31	3·50		1 668	3 450
H, CH_3	73	(399·5)	90·07	6·40	3·47		1 598	3 415
IIc	165—169	$C_{29}H_{22}NCl$	82·93	5·28	3·34	8·44	1 668	3 450
H, Cl	73	(419·9)	83·08	5·30	3·28	8·39	1 598	3 410
IId	147—151	$C_{29}H_{22}NBr$	75·00	4·77	3·02	17·21	1 665	3 450
H, Br	62	(464·4)	75·10	4·80	2·96	17·10	1 598	3 410
IIe	172—178	$C_{31}H_{27}N$	90·03	6·58	3·39		1 665	3 450
CH_3, H	83	(413·6)	90·03	6·69	3·30		1 595	3 418
IIf	192—195	$C_{29}H_{21}NBr_2$	64·09	3·90	2·58	29·42	1 665	3 448
Br, H	93	(543·3)	63·90	3·80	2·53	29·40	1 590	3 405
IIg	192—196	$C_{29}H_{21}NF_2$	82·64	5·02	3·32	9·02	1 668	3 452
F, H	70	(421·5)	82·74	5·11	3·20	8·88	1 603	3 410
IIIb	157—161	$C_{31}H_{27}N$	90·03	6·58	3·39		1 658	
H, CH_3	70	(413·6)	90·15	6·68	3·27		1 595	
IIIc	176—180	$C_{30}H_{24}NCl$	83·03	5·57	3·23	8·17	1 658	
H, Cl	56	(433·9)	82·64	5·66	2·99	7·98	1 596	
IIId	170—174	$C_{30}H_{24}NBr$	75·31	5·06	2·93	16·70	1 657	
H, Br	61	(478·4)	75·36	5·16	2·74	16·62	1 595	
IIIg	165—170	$C_{30}H_{23}NF_2$	82·74	5·32	3·22	8·32	1 660	
F, H	51	(435·5)	82·60	5·30	3·20	8·40	1 602	
IVb	56—58	$C_{30}H_{24}O$	89·97	6·04			1 680	(1 220)
H, CH_3	42	(400·5)	90·03	6·11			1 640	(1 180)
IVc	115—120	$C_{29}H_{21}OCl$	82·75	5·03		8·42	1 680	(1 220)
H, Cl	55	(420·9)	82·61	5·12		8·42	1 638	(1 179)
IVd	101—105	$C_{29}H_{21}OBr$	74·84	4·55		17·17	1 680	(1 220)
H, Br	83	(465·4)	74·88	4·62		16·98	1 638	(1 179)
IVg	235—237	$C_{29}H_{20}OF_2$	82·45	4·77		8·99	1 680	(1 215)
F, H	52	(422·5)	82·50	5·00		9·10	1 639	(1 162)
V	156—157	$C_{29}H_{22}S$	86·53	5·51	7·96[b]		1 680	
H, H	50	(402·6)	86·40	5·57	8·00[b]		1 640	

[a] X refers to halogen; [b] refers to sulfur.

RESULTS AND DISCUSSION

The IR spectra of chloroform solutions of compounds *II* and *III* revealed vibrations of dihydropyridine ring characteristic of two approximately equal medium intense bands at 1 657–1 668 and 1 595–1 603 cm^{-1}. Stretching vibrations of the N—H bond for compounds *IIa–IIg* also occured as two equally intense bands at 3 448 to 3 452 and 3 410–3 418 cm^{-1}, thus indicating a defined association of molecules in solution. Similarly, 4*H*-pyrans *IVb–IVd*, *IVg* and 4*H*-thiopyran *V* showed skeletal vibrations of the heterocyclic ring as two diagnostic bands; the more intense lay at 1 680 and the less intense one at 1 638–1 640 cm^{-1}. Vibrations in the 1 162 to 1 220 cm^{-1} range of pyrans *IVb–IVd*, *IVg* were ascribed to stretching vibrations of the C—O bond.

The ^{1}H NMR signals of aromatic rings of compounds *IIa–IIg*, *IIIb–IIIg*, *IVa–IVh*, and *V* (Table II) were interpreted by analogy with the spectrum of *IIIa*, where the signals under consideration were assigned from the 2 D-COSY, HETCOR and RELAY experiments. The paramagnetically most shielded four *ortho*-protons H-2b at the aromatic ring of all heterocycles formed a multiplet with coupling constants ^3J within 6·8 and 8·9 Hz and ^4J within 1·4 and 1·8 Hz. Signals of *meta*-protons H-2c at the aromatic ring appeared in a stronger field as triplets with the 2,6-diphenyl-substituted heterocycles *a–d* and as doublets with 2,6-*para*-diphenyl-substituted heterocycles *e–h* excepting the fluorinated derivatives *g*, which formed triplets. Signals of derivatives *e*, *g*, *h* were, in accord with the additive rules[7], shifted towards a higher field. These signals were in some cases overlapped by triplets of the *para*-protons H-2d thus making the reading of coupling constant impossible. The proton signals H-4 of aromatic rings bonded to a quaternary sp^3 carbon C-4 are little less shielded. Multiplets of these protons overlaped more or less each other and with compounds *b–d* their number even rose due to an asymmetric substitution. Triplets of the *para*-aromatic protons H-4d were at least downfield shifted and in some cases they were well discerned from other signals. Chemical shifts of olefinic protons H-3 and H-5 of dihydropyridines *IIa–IIg* and *IIIa–IIIg* were at δ 5·09 to 5·29, those of 4*H*-pyrans *IVa–IVh* at δ 5·62–5·76 due to a higher electronegativity of the heteroatom, whilst those of 4*H*-thiopyran *V* at δ 6·24. A smaller sweep width in this chemical shift region of compounds *IIa–IIg* displayed splitting of these signals to a doublet. The COSY experiment showed this splitting to be associated with an interaction with the N–H proton (^4J = 1·1 Hz); this finding was backed by the fact that with compounds *III*, *IV* and *V*, where such an interaction does not exist, splitting was not observed. Signal of the N–H proton for compounds *IIa–IIg* appeared in the δ range 4·60–5·11 and its position was strongly dependent on temperature and mainly on the solvent used; in $(CD_3)_2SO$ e.g., this signal of *IIa* was downfield shifted up to 2·76 ppm.

Like in the ^{1}H NMR spectra also in the ^{13}C NMR spectra of compounds *IIa–IIg*, *IIIb–IIIg*, *IVa–IVh* and *V* (Table III) all signals in the aromatic region were inter-

TABLE II

^{1}H NMR spectral data (δ, ppm (^3J, Hz)[a]) of 4*H*-pyranoid heterocycles *IIa*—*IIg*, *IIIa*—*IIIg*, *IVa*—*IVh*, and *V*

Compound	N–H N–CH_3	H-2b	H-2c	H-2d	H-3b	H-4b	H-4c	H-4d
IIa[c]	7·74	7·66(7·0)	7·40(7·0)	7·36(7·1)	5·12	7·26(7·5)	7·32(7·5)	7·15(7·2)
IIa[d]	4·98	7·43(7·0)	7·35 —[e]	7·24 —[e]	5·24		6·99—7·23[f]	
IIb[d]	4·96	7·46(7·3)	7·35 —[e]	7·23 —[e]	5·25		6·90—7·20[f]	—[g]
IIc[d]	4·99	7·34(8·1)	7·27 —[e]	7·22(7·4)	5·10		6·89—7·20[f]	
IId[d]	4·98	7·34(8·0)	7·28 —[e]	7·21 —[e]	5·09		6·82—7·20[f]	
IIe[d]	5·11	7·53(8·0)	7·28(8·0)	—[h]	5·25		6·93—7·25[f]	
IIf[d]	4·60	7·35(8·0)	7·25(8·0)	—	5·10		6·88—7·20[f]	
IIg[d]	4·78	7·43(8·1)	7·27(8·1)	—	5·14		6·74—7·20[f]	
IIIa[c]	2·51	7·57(7·1)	7·43(7·1)	7·37(7·2)	5·31	7·27(7·5)	7·32(7·5)	7·17(7·2)
IIIa[i]	2·60	7·55(7·2)	7·37(7·2)	7·32 —[e]	5·27		7·28—7·31[f]	7·16(7·0)
IIIb[i]	2·60	7·56(7·1)	7·37(7·1)	7·34 —[e]	5·27		7·11—7·32[f]	7·16(6·8)[j]
IIIc[i]	2·60	7·54(6·8)	7·41 —[e]	7·36 —[e]	5·21		7·16—7·35[f]	
IIId[i]	2·60	7·54(6·8)	7·41 —[e]	7·36 —[e]	5·20		7·19—7·35[f]	

IIIe[i]	2·59	7·43(8·0)	7·17(8·0)	—[k]	5·23	7·26—7·33[f]	7·15(6·5)
IIIf[i]	2·54	7·49(8·5)	7·40(8·5)	—	5·29	7·26—7·32[f]	7·17(6·7)
IIIg[i]	2·56	7·50(8·7)	7·05(8·7)	—	5·25	7·21—7·32[f]	7·17 —[e]
IVa[c]		7·82(7·3)	7·45(7·3)	7·38(7·0)	6·05	7·33(6·4) 7·34(6·4)	7·20(6·3)
IVa[i]		7·77(7·0)	7·40(7·0)	7·36 —[e]	5·76	7·28—7·34[f]	7·19 —[e]
IVb[i]		7·76(7·0)	7·39(7·0)	7·35 —[e]	5·75	7·13—7·32[f]	—[e]
IVc[i]		7·75(7·2)	7·40(7·2)	7·37 —[e]	5·71	7·19—7·36[f]	
IVd[i]		7·75(7·1)	7·43(7·1)	7·39 —[e]	5·72	7·18—7·38[f]	
IVe[i]		7·64(8·2)	7·18(8·2)	—[m]	5·69	7·30—7·32[f]	7·19 —[e]
IVf[i]		7·59(8·7)	7·52(8·7)	—	5·74	7·24—7·35[f]	7·22(6·9)
IVg[i]		7·70(8·7)	7·08(8·7)	—	5·68	7·29—7·36[f]	7·22(6·7)
IVh[i]		7·68(8·9)	6·91(8·9)	—[n]	5·62	7·29—7·33[f]	7·20 —[e]
V[i]		7·57(7·4)	7·35(7·4)	7·33 —[e]	6·24	7·20—7·32[f]	

[a] Coupling constants ^4J were within 1·4 and 1·8 Hz; [b] signals of compounds *IIa*—*IIg* were doublets, $^4J = 1{\cdot}1$ Hz; [c] measured in $(CD_3)_2SO$; [d] measured in $C_6D_5CD_3$; [e] overlapping signals, the coupling constant was unreadable; [f] unresolved multiplet; [g] signal of the CH_3 group appeared at δ 2·18; [h] CH_3 groups at δ 2·16; [i] measured in $CDCl_3$; [j] signal of the CH_3 group at δ 2·33; [k] CH_3 group at δ 2·36; [l] CH_3 group at δ 2·35; [m] CH_3 group at δ 2·35; [n] CH_3 groups at δ 3·82.

TABLE III

^{13}C NMR chemical shift data (δ, ppm) of 4*H*-pyranoid heterocycles *IIa*—*IIg*, *IIIa*—*IIIg*, *IVa*—*IVh*, and *V* as measured in $CDCl_3$ (compounds *IIa*—*IIg* in $C_6D_5CD_3$)

Compound[a]	C-2	C-2a	C-2b	C-2c	C-2d	C-3	C-4	C-4a	C-4b	C-4c	C-4d
IIa	138·07	136·31	125·85	128·83	128·59	104·62	50·74	152·26	128·34	128·53	125·80
								152·42	128·30	128·59	125·77
IIb	138·11	136·16	125·82	128·82	128·50	104·82	50·40	149·46	128·70	129·28	134·91[b]
								152·69	129·63	129·66	126·97
IIc	138·78	137·50	126·80	129·47	129·63	104·92	51·30	151·68	129·85	130·99	132·73
								151·65	126·00	128·87	125·84
IId	137·81	136·57	125·84	128·50	128·55	103·88	50·41	151·18	130·41	131·64	120·95
IIe	137·87	136·21	125·73	128·45	135·42[c]	104·05	50·76	152·41	128·67	129·50	125·68
IIf	137·49	135·23	128·63	132·02	124·89	105·36	50·62	151·66	127·30	128·56	126·07
IIg	135·31	133·95[d]	128·63[d]	115·68[d]	163·11[d]	104·87	50·70	151·98	127·60	128·63	126·01
IIIa[e]	143·34	138·06	127·99	128·27	127·99	112·32	49·46	151·44	127·78	128·14	125·53
								151·20	127·98	128·14	125·50
IIIb[f]	143·23	138·08	127·88	127·28	127·88	112·54	49·06	151·13	127·96	128·88	135·03
								150·93	128·12	128·26	125·74
IIIc[g]	143·50	137·81	127·89	128·34	127·89	111·60	49·11	150·08	128·26	129·42	131·38
								150·88	128·16	128·27	125·75

IIId[h]	143·60	137·81	127·90	128·34	127·90	111·50	49·20	150·61	129·85	131·22	119·56
IIIe[i]	143·20	137·70	127·76	128·91	135·23	111·64	49·38	151·59	127·98	128·06	125·40
IIIf[j]	142·34	136·73	129·35	131·53	122·01	113·17	49·42	150·86	127·89	128·28	125·77
IIIg[k]	142·39	133·93[d]	129·46[z]	115·33[d]	162·72[d]	112·65	49·43	151·22	127·94	128·26	125·71
IVa	147·03	134·29	124·78	128·39	128·53	104·00	47·35	149·52	127·92	128·35	126·14
								149·66	127·92	128·23	125·31
IVb	146·91	134·39	124·80	128·36	128·50	104·14	46·99	146·73	126·10	129·11	135·73[l]
								149·06	127·88	128·71	126·39
IVc	147·37	134·17	124·86	128·55	128·74	103·57	47·10	148·19	129·09	129·39	132·12
								149·03	127·89	128·80	126·46
IVd	147·43	134·18	124·90	128·50	128·61	103·52	47·2	148·75	129·85	131·56	120·33
IVe	147·10	131·64	124·72	129·03	138·40[m]	103·24	47·31	149·77	127·94	128·34	126·05
IVf	146·20	133·08	136·36	131·60	122·72	104·55	47·35	149·04	127·86	128·53	126·38
IVg	146·33	130·55[d]	126·68[d]	115·39[d]	163·04[d]	103·93	47·36	149·37	127·89	128·50	126·30
IVh	146·86	127·17	126·17	113·79	159·97[n]	102·55	47·33	149·92	127·93	128·34	126·03
V	138·50	131·31	126·64	128·57	128·54	123·85	53·42	148·38	128·19	128·44	126·33

[a] For numbering of carbon atoms cf. formulae *II*—*V*; [b] CH_3 group at δ 21·01; [c] CH_3 group at δ 21·26; [d] signals of the *p*-fluorophenyl group formed doublets with coupling constants J(C, F) within 3·0 and 4·0 Hz for C-2a, 8·0 Hz for C-2b, 22·1—32·2 Hz for C-2c, and 246·5 to 248·5 Hz for C-2d; [e] N–CH_3 group at δ 38·32; [f] N–CH_3 group at δ 38·34 and CH_3 group at δ 20·97; [g] N–CH_3 group at δ 38·21; [h] N–CH_3 group at δ 38·20; [i] N–CH_3 group at δ 38·12 and CH_3 groups at δ 21·18; [j] N–CH_3 group at δ 38·33; [k] N–CH_3 group at δ 38·16; [l] CH_3 group at δ 20·96; [m] CH_3 groups at δ 21·23; [n] OCH_3 groups at δ 65·35.

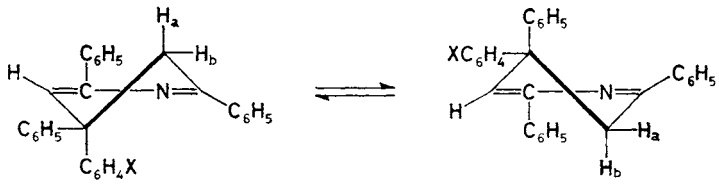
preted by analogy with compound *IIIa*. The most significant paramagnetic shift displayed signals of quaternary carbons of the aromatic ring C-4a, which were for compounds *b*–*d* duplicated due to magnetic non-equivalence of both phenyl rings and consequently, their intensity was halved. Further quaternary carbons C-2 and C-2a of the aromatic ring appeared at higher field, where electronic effects of the neighbouring heteroatom became more effective. The sequence of individual derivatives in the region of tertiary carbons of the aromatic ring was considerably influenced by the nature of the substituent at aromatic ring; the chemical shift values corresponded approximately to additive rules[8]. The electronic effects of heteroatoms were manifested mostly by the chemical shifts of tertiary carbons C-3 and C-5, which were located at δ 103·88–104·92 for dihydropyridines *IIa*–*IIg* and 4*H*-pyrans *IVc*–*IVh*, and at δ 111·50–113·17 for dihydropyridines *IIIa*–*IIIg*. These signals were strongly shifted up to δ 123·85 for 4*H*-thiopyran *V*, this being evidently due to steric interactions with the 3*d* orbital-electrons in the valence sphere of the sulfur atom; these orbitals are, on the other hand, vacant for oxa and azaanalogues *II*–*IV*. Electronic effects of the heteroatom were far less seen on the chemical shifts of quaternary sp^3 carbons C-4: they appeared at δ 50·40–51·30, 49·06–49·46, and 46·99–47·36 with compounds *IIa*–*IIg*, *IIIa*–*IIIg*, and *IVa*–*IVh*, respectively. This signal lay at δ 53·42 with the 4*H*-thiopyran *V*. Chemical shifts of the fluorophenyl group of fluorinated derivatives *g* were recorded as centers of doublets with coupling constants J(C, F) 3·0–4·0 Hz for carbons C-2a, 8·0 Hz for carbons C-2b, 22·1 to 32·2 Hz for carbons C-2c, and 246·5–248·5 Hz for carbons C-2d.

The ^{19}F NMR spectra of compounds *IIg* in $(CD_3)_2SO$ showed a signal at δ −114·05 ascribable to the 1,4-dihydro tautomer and two minor ones in a 1 : 1 ratio located at δ −114·52 (fluorine at C-6d) and −109·78 (fluorine at C-2d), corresponding to an asymmetric 3,4-dihydro tautomer *VIg* (cf. the next paragraph). The ^{19}F NMR proton decoupled spectra of *IIIg* and *IVg* in $CDCl_3$ also displayed singlets at δ −113·90 and −106·28, thus evidencing their symmetry in solution.

1,4–3,4-*Dihydropyridine Tautomerism*

Although the proton tautomerism of nitrogen-containing heterocycles is well known, its occurence with dihydropyridines has not been experimentaly proved[2,3] as yet. Dihydropyridine *IIa*, known for a longer time[9] appeared, as we have found by spectroscopic investigation, in a dynamic equilibrium with its 3,4-dihydro tautomer *VIa*. Maeda and coworkers[10], examined a similar tautomerism with the topologically analogous tetraphenyl-2,3(2,5)-dihydro-1,3,5-triazine which could be considered the 3,5-diaza analogue of *IIa*. The ^{1}H NMR spectra of compounds *IIa*–*IIg* (Table II) measured in $C_6D_5CD_3$ contained signals of olefinic protons H-3 and H-5, and the N–H protons in addition to minor signals at δ 2·92–3·11, and 6·30–6·47 in a 2 : 1 ratio; their intensity increased with the increasing temperature. These signals were attributed to methylene protons H-3 and the olefine proton H-5 of 3,4-dihydro

tautomers *VIa – VIg* (Table IV). Further minor signals of two multiplets in a 1 : 1 ratio found in the region of protons bound to aromatic ring were ascribed to *o*-protons H-2b and H-6b of compounds *VIa – VIg*. Their coupling constants ^3J and ^4J were between 7·8 and 8·8 Hz, and 1·4 – 1·8 Hz, respectively. These signals were downfield shifted when contrasted with the analogous signals of *IIa – IIg*; due to molecular symmetry they were not isochronous. The remaining signals of protons at aromatic ring of compounds *VIa – VIg* were overlapped by those of their 1,4-dihydro tautomers *IIa – IIg*. The asymmetrically substituted dihydropyridines *IIb – IId* displayed splitting of the prochiral protons of the methylene group H-3 into an AB pattern which coalesced with a temperature increase. This phenomenon can be rationalized by an accelerating exchange of H_a and H_b protons between two conformers by temperature increase, as illustrated in Scheme 1.



SCHEME 1

TABLE IV

^{1}H NMR spectral data (δ, ppm (^3J, Hz)[a]) of 3,4-dihydropyridines *VIa – VIg* in $C_6D_5CD_3$

Compound[b]	H-2b	H-3	H-5	H-6b
VIa	7·95 (7·8)	3·11	6·44	8·00 (7·9)
VIb[c]	7·97 (7·8)	3·10[d]	6·47	8·02 (7·5)
VIc	7·93 (8·5)	2·99[d]	6·30	8·02 (8·4)
VId	7·92 (8·4)	2·98[d]	6·30	8·03 (8·3)
VIe[e]	7·97 (8·1)	3·12	6·43	8·09 (8·1)
VIf	7·55 (8·8)	2·92	6·30	7·63 (8·8)
VIg	7·77 (8·8)	3·07	6·31	7·81 (8·8)

[a] Coupling constants ^4J were within 1·4 and 1·9 Hz; [b] other signals in the aromatic region were overlapped by signals of 1,4-tautomers II; [c] signal of the CH_3 group appeared at δ 2·06; [d] AB pattern at 297 K coalesced up to 373 K; [e] CH_3 groups at δ 2·30 and 2·09.

Tautomerism *II* ⇄ *VI* was now examined by ^{1}H NMR spectroscopy at various temperatures in various solvents. As found, aprotic strongly polar solvents able to interact with the N–H proton, as e.g. dimethyl sulfoxide are unsuited for such a study because the strong solvatation (formation of N—H···O—S bonds) shifted the equilibrium *II* ⇄ *VI* almost exclusively to the left side thus hindering formation of the 3,4-dihydro-form *VI* the abundance of which virtually did not undergo change either at elevated temperature. Suitable were shown to be little polar aromatic or halogenated hydrocarbons as e.g. benzene, toluene or chloroform. In other solvents as e.g. in dioxane, methanol, ethanol, acetone or acetic acid compounds *IIa*–*IIg* are sparingly soluble, whereas with some others they even react (trifluoroacetic acid, cf. the last chapter). Temperature dependence of the above-mentioned tautomerism was examined by the ^{1}H NMR spectra of compounds *IIa*–*IIg* in $C_6D_5CD_3$ at 297, 320, 344, and 373 K. The intensity ratio of proton signals H-3–H-5 to H-3–H-5 of compounds *IIa*–*IIg* and *VIa*–*VIg* were decisive for the equilibrium tautomeric *II* ⇄ *VI* constants K_t, which are presented in Table V together with the approximate values of thermodynamic variables ΔH, ΔS, and ΔG_{298} calculated by reggression analysis. It is evident that the 3.4-dihydro tautomer *VI* is thermodynamically less stable, this being in line with the theoretical *ab initio* 4-31G MO calculations[11] based upon models of unsubstituted dihydropyridines.

Tautomerism *II* ⇄ *VI* could well be seen also in the ^{13}C NMR spectra of *IIa*–*IIg* measured in $C_6D_5CD_3$. Minor signals of compounds *VIa*–*VIg* are listed in Table VI. The most noticeable difference between compounds *II* and *VI* was observed with carbon atoms C-3, having their chemical shifts at δ 30·30–38·60. The 3,4-dihydro tautomers also revealed a weak upfield shift of C-4; its signal appeared at δ 38·36 to 47·80. The presence of an olefinic C=N bond of the 3,4-dihydro-form *VI* was mani-

TABLE V

Values K_t, ΔH, ΔS, and ΔG_{298} for tautomerism *II* ⇄ *VI* in $C_6D_5CD_3$

R^1	R^2	K_{297}	K_{320}	K_{344}	K_{373}	ΔH kJ mol^{-1}	ΔS J mol^{-1} . K^{-1}	ΔG kJ mol^{-1}
H	H	0·33	0·35	0·37	0·40	2·3	−1·6	2·8
H	CH_3	0·23	0·25	0·28	0·30	3·4	−1·0	3·7
H	Cl	0·24	0·27	0·32	0·37	5·4	6·2	3·6
H	Br	0·46	0·53	0·55	0·60	3·1	4·0	1·9
CH_3	H	0·20	0·28	0·33	0·41	8·3	14·9	3·9
Br	H	0·66	0·71	0·74	0·76	1·8	2·6	1·0
F	H	0·22	0·27	0·33	0·44	8·2	14·9	3·8

TABLE VI

^{13}C NMR spectral data (δ, ppm) of 3,4-dihydropyridines *VIa*—*VIg* at 297 K

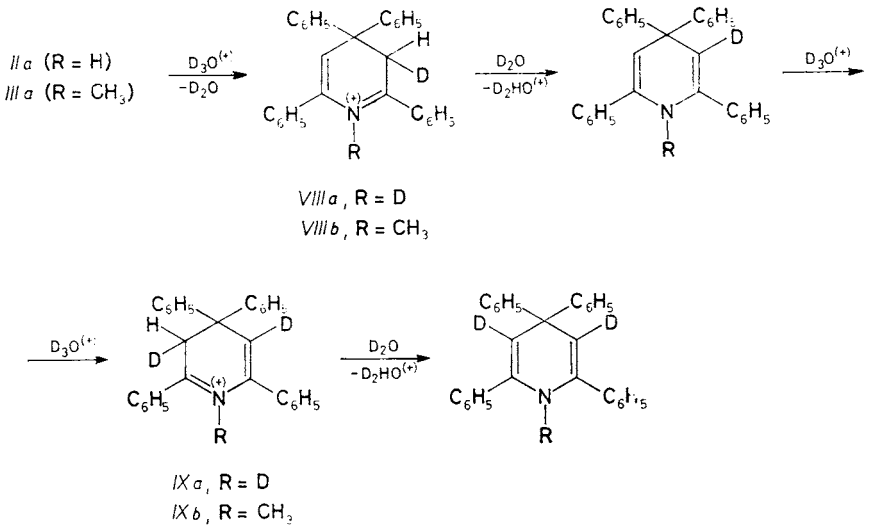
Compound[a]	C-2	C-2a	C-3	C-4	C-4a	C-5	C-6	C-6a	C_{Ar}
VIa	165·10	147·10	37·85	47·45	153·00	118·26	140·80	133·20	126·45—132·00
VIb[b]	164·29	147·73	30·30	38·35	152·00[c]	118·61	139·57	136·22	125·81—130·48
VIc	164·87	147·77	38·60	47·80	152·69[d]	118·55	139·94	133·77	126·97—132·73
VId	163·89	146·75	37·58	46·91	145·79[e]	117·49	138·98	138·90	124·89—130·86
VIe[f]	163·64	145·12	37·90	47·30	147·39	117·10	140·52	136·64	126·40—129·34
VIf	163·29	143·96	37·44	47·19	146·61	118·90	137·68	—[g]	126·07—131·91
VIg	163·30	143·60	37·81	46·86	146·10	117·90	138·00	—[g]	126·95—129·58

[a] For numbering of carbon atoms see formula *VI*; [b] measured at 373 K; [c] signal for the *p*-tolyl group appeared at δ 114·16; [d] *p*-chlorophenyl group at δ 146·27; [e] *p*-bromophenyl group at δ 145·32; [f] CH_3 groups at δ 21·21 and 21·26; [g] overlapping signals.

fested by a downfield shift of the quaternary sp^2 C-2 carbons and quaternary C-2a carbons of the aromatic ring. Tertiary C-5 atoms were downfield shifted to δ 117·10 to 118·90 when compared with the analogous atoms of compounds *IIa*–*IIg*. The situation is more complicated in the region characteristic of C-2b to C-2d, and C-4b to C-4d, respectively, where these signals were overlapped by those of the solvent or compounds *II* and therefore, only the chemical shift interval without any assignment is listed in Table VI.

Deuteriodeprotonation of Compounds IIa *and* IIIa

Addition of D_2O to the solution of *IIa* in $(CH_3)_2SO$ did not cause changes in the ^1H NMR spectrum measured after 2 h with the exception of the N–H proton. A clear exchange of the proton for deuterium took place after acidification with a drop of deuteriotrifluoroacetic acid; this was accompanied by disappearance of very weak proton signals H-3 and H-5 of the 3,4-dihydro tautomer *VIa* which almost totally disappeared also with the 1,4-dihydro tautomer *IIa* together with the N—H signal. The ^{13}C NMR spectrum reflected the deuteriodeprotonation by a very strong collaps of the olefinic C-3 and C-5 carbon signals under formation of a triplet at δ 102·35 (J(C, D) = 26 Hz). An interesting substitution effect of deuterium was observed even with the quaternary C-4 atom, for which the signal was upfield shifted with respect to the non-deuteriated compound *IIa*, and occured at δ 48·93. Like in the ^1H NMR spectrum of *IIIa* recorded in C_6D_6 neither here any change was seen after addition of D_2O, because deuteriodeprotonation proceeded only after



SCHEME 2

acidification. The spectrum was lacking signals of olefinic H-3 and H-5 protons at δ 5·43, whilst a new diffuse peak corresponding to water appeared. The main reaction channel of deuteriodeprotonation under study can be seen in Scheme 2. Migration of deuterium among positions 1, 3, 5 of compound *IIa* can also be explained by tautometrism *IIa* ⇄ *VIa*.

Reaction of Compounds IIa *and* IIIa *with Trifluoroacetic Acid*

Addition of trifluoroacetic acid to a solution of *IIa* in $CDCl_3$ in the spectrometer cuvette caused disappearance of H-3 and H-5 signals of both the 1,4- (*IIa*) and 3,4--dihydro tautomers *VIa* in the ^{1}H NMR spectrum. Instead, two new singlets appeared at δ 4·13 and 6·75 in a 2 : 1 ratio. This new compound was assigned the structure of 3,4-dihydropyridinium salt *VIIa*, which originated through protonation of dihydropyridine *IIa*; the same product would be created by protonation of 3,4-dihydro tautomer *VIa* as well. Substitution effect of the positive charge was manifested in the spectrum *VIIa* by a strong deshielding of H-2b signals at the aromatic ring (Table VII). The positive charge, which can be delocalized, was associated with a downfield shift of H-3 and H-5 signals when compared with those of the 3,4-dihydro tautomer *VIa*. An identical ^{1}H NMR spectrum with that of compound *VIIa* was encountered when dihydropyridine *IIa* was reacted with an excess of trifluoroacetic acid, and the spectrum in $CDCl_3$ was taken after the acid had been removed. Addition of trifluroacetic acid to *IIIa* in $CDCl_3$ led to compound *VIIb*, the ^{1}H NMR spectrum of which resembled that of *VIIa* (Table VII). The ^{13}C NMR spectra of 3,4-dihydropyridinium salts *VIIa*, *VIIb* showed nine tertiary and four quaternary

TABLE VII

^{1}H NMR spectral data (δ, ppm (^3J, Hz)[a]) of *VIIa*, *VIIb*—*IXa*, *IXb*

Compound	H-3	H-5	H-2b	H-2c	H-2d	H_{Ar}
VIIa[b]	4·13	6·75	7·97(7·6)	7·59(7·6)	7·77(7·1)	7·21—7·53
VIIIa[c]	4·29	7·01	8·07(7·6)	7·75(7·6)	7·95(7·1)	7·28—7·58
IXa[c]	4·25	—	8·07(7·6)	7·75(7·6)	7·95(7·1)	7·28—7·58
VIIb[b,d]	4·21	6·77	7·56 —[f]	7·58 —[f]	7·71(7·5)	7·27—7·47
VIIIb[c,e]	4·25	6·89	7·63 —[f]	7·67(7·9)	7·78(7·4)	7·35—7·50
IXb[c,e]	4·10	—	7·63 —[f]	7·67(7·9)	7·78(7·4)	7·35—7·50

[a] Coupling constants ^4J were within 1·1—1·7 Hz; [b] measured in $CDCl_3$ after addition of one drop CF_3COOH; [c] measured in CF_3COOD; [d] CH_3 group at δ 3·52; [e] CH_3 group at δ 3·57; [f] overlapping signals, coupling constant was unreadable.

carbons of the aromatic ring at δ 144·42–128·14. The C-4 quaternary carbons resonated at δ 42·50 and 45·80 for compounds *VIIa* and *VIIb*, respectively. Carbons C-3 and C-5 were downfield shifted similarly as the corresponding protons when contrasted with the same nuclides of the 3,4-dihydro tautomer *VIa*. They resonated at δ 48·16, 46·39 and 144·42, 135·67 for compounds *VIIa* and *VIIb*, respectively. Signal of the N–CH_3 group of compound *VIIb* lay at δ 44·85 and its downfield shift with respect to the analogous signal of dihydropyridine *IIIa* was caused by the effect of positively charged nitrogen.

A more complicated situation emerged when recording the ^{1}H NMR spectrum in deuteriotrifluoroacetic acid as solvent, since a successive deuteriodeprotonation of 3,4-dihydropyridinium salts being formed can take place as illustrated in Scheme 2. Measurement of temperature dependence of the ^{1}H NMR spectrum showed that at least three compounds were in the cuvette; their ratio altered with the increasing temperature. Thus, signals analogous to those of compound *VIIa* at 7·01 and 4·29 in a 1 : 1 ratio were observed at 20°C. This finding met requirements for the structure *VIIIa*, where deuterium from deuteriotrifluoroacetic acid was added to C-3 and the intensity of the H-3 proton signal was halved. The signal at 4·25 was attributed to the methylene proton H-3 of 3,5-deuterio-derivative *IXa*. Temperature rise to 40°C caused weakening of signals associated with this position for compound *VIIIa* and enhanced their intensity for compound *IXa* due to deuteriodeprotonation *VIIIa* → *IXa*. The mutual *VIIIa* to *IXa* ratio was found to be 1: 1 at 20°C and 1 : 3 at 40°C. Further elevation to 60°C resulted in weakening of signals for *IXa* evidently due to transition *IXa* → *Xa*. As follows, the successive deuteriodeprotonation is an overall thermodynamically controlled process, the fastest step of which is the exchange of a proton for deuterium at N-1, whereas deuteration of *VIIIa* first of all proceeded at the olefinic proton H-5 and after a longer time, or even at more elevated temperature the last proton H-3 of compound *IXa* was exchanged. A similar situation as described for compound *IIa* was also encountered after measuring the ^{1}H NMR spectrum of *IIIa* in deuteriotrifluoroacetic acid showing the formation of deuteriated products *VIIIb* – *Xb* (Table VII).

REFERENCES

1. Kurfürst A., Zelený J., Schwarz M., Kuthan J.: Chem. Papers *41*, 623 (1987).
2. Kuthan J., Kurfürst A.: Ind. Eng. Chem., Prod. Res. Dev. *21*, 191 (1982).
3. Sausios A., Duburs G.: Heterocycles *27*, 269, 991 (1988).
4. Kuthan J.: Adv. Heterocycl. Chem. *34*, 145 (1983).
5. Suld G., Price Ch. C.: J. Am. Chem. Soc. *84*, 2094 (1962).
6. Parasaran T., Price Ch. C.: J. Org. Chem. *29*, 946 (1964).
7. Pretsch E., Clerc T., Seibl J., Simon W.: *Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Methoden.* Springer Verlag, Heidelberg 1981.

8. Levy G. C., Nelson G. L.: *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists.* Wiley-Interscience, New York 1972.
9. Peres de Carvalho A.: C. R. Acad. Sci. *199*, 1430 (1934).
10. Maeda K., Kihara N., Ishimura N.: J. Chem. Soc., Perkin Trans. 2, *1985*, 887.
11. Böhm S., Kuthan J.: Collect. Czech. Chem. Commun. *46*, 2068 (1981).

Translated by Z. Votický.